# Studies on the stability of the cyclobutane b-aminoacid skeleton : a cautionary tale

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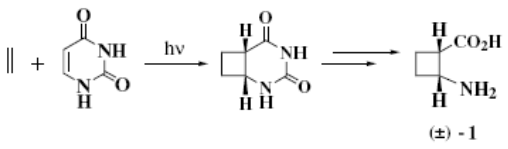
**Abstract**—The 2-amino-1-cyclobutanecarboxylic acid skeleton undergoes facile retro-Mannich type ring opening in solution, which may lead to unexpected by-products during its synthesis or manipulation.

As a contribution to the rapidly expanding family of constrained β-aminoacids, we recently described the short and efficient synthesis of (±)-*cis*-2-amino-1-cyclobutanecarboxylic acid **1** via a [2+2] photocycloaddition strategy (Scheme 1).[1] Our NMR spectroscopic data for product (±)-**1** were consistent with those reported in 1982 by Kennewell et al.,[2] but differed from those published more recently by the Ortuño group[3] for the (1*R*,2*S*) enantiomer, described as having a specific optical rotation of −9. This was rather confusing, since both recent syntheses seemed to be validated by X-ray crystallographic studies: for our part, with a benzamide derivative of the final product,[1] and with a dipeptide derivative of the immediate synthetic precursor of (−)-**1** in the other case.[3] Given the recent interest in such structures,[1–4] we decided to carry out a detailed study to clear up this ambiguity, and have thus revealed the remarkable ease with which the parent skeleton may undergo ring opening.




**Scheme 1.**

*Keywords*: β-Aminoacid; Cyclobutane; Retro-Mannich reaction.

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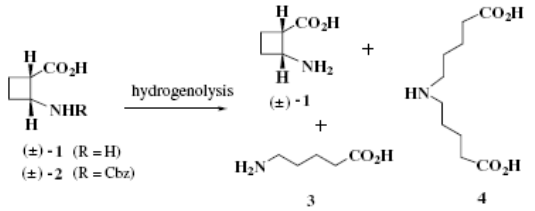
The final step of the Ortuño group's synthesis was the catalytic hydrogenolysis of the benzylcarbamate derivative (−)-**2**. We prepared racemic **2** from our own samples of (±)-**1**, and submitted it to hydrogenolysis (Scheme 2; Table 1).

Under the proposed literature conditions (2 atm $H_2$, 10% Pd–C, MeOH, rt, 16 h), a mixture of three aminoacid products was obtained, of which the *least* abundant one presented NMR data identical to those of the expected product **1**. One of the two remaining compounds was found to be spectroscopically identical with

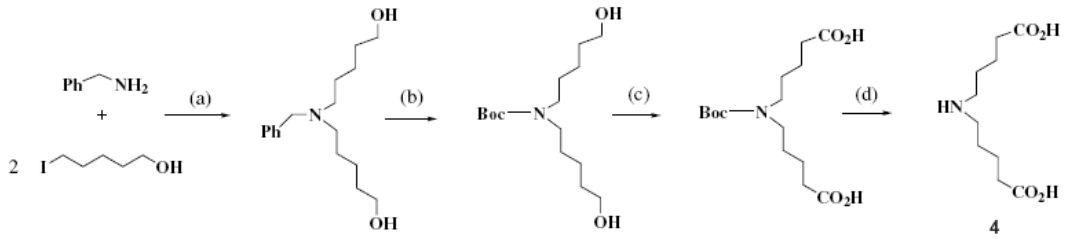



**Scheme 2.**

**Table 1**

| R | Compound | Conditions | Results % (±)-**1**–% **3**–% **4** |
|---|---|---|---|
| Cbz | (±)-**2** | **A*** | 16–35–49 |
| H | (±)-**1** | **A** | 4–36–60 |
| H | (±)-**1** | **B** | 0–25–75 |

Conditions **A**: 2 atm $H_2$, 10% Pd–C, MeOH–$H_2O$, rt, 16 h (*: MeOH only). Conditions **B**: 3 atm $H_2$, 20% $Pd(OH)_2$–C, MeOH–$H_2O$, rt, 3 days.




**Scheme 3.** Reagents and conditions: (a) $K_2CO_3$, EtOH, reflux, 5 h, 69%; (b) $H_2$, $Pd(OH)_2$–C, $Boc_2O$, EtOAc–EtOH, rt, 24 h, 69%; (c) PDC, DMF, rt, 6 h, 43%; (d) TFA, $CH_2Cl_2$ rt, 30 min, 80%.

a commercial sample of 5-aminopentanoic acid, **3**, while the most abundant component was identified as **4**, by comparison with an authentic sample prepared according to Scheme 3.

We tested the stability of the β-aminoacid (±)-**1** under hydrogenation conditions (Table 1). Using Ortuño's conditions, most of the sample was transformed into a mixture of **3** and **4** after 16 h; under more forcing conditions (3 atm $H_2$, 20% $Pd(OH)_2$–C, 3 days) the transformation was complete.

Of the three compounds, the NMR chemical shifts obtained ($D_2O$ solution) for **4**[5] are the closest to those previously published for (−)-**1**.[3] These results clearly suggest that the product previously thought to be (−)-**1** was probably a mixture of (−)-**1**, **3** and **4**, with the latter predominating; the observation of a nonzero optical rotation indicates that at least some of the expected compound was present. Hydrogenation alone does not explain the formation of **3** and **4** from **2**. Indeed, hydrogenolysis of a cyclobutane ring to give an acyclic product usually requires forcing conditions. In a recent example of the four-membered ring's stability, straightforward hydrogenolytic *N*- and/or *O*-debenzylations of *cis*-2-aminocyclobutanols were carried out without ring opening.[6] Further investigation was therefore required.

In order to pursue our studies, we used the α-methylbenzyl derivative **5**,[7] which incorporates a useful 'molecular location' moiety as its N-substituent. An aqueous solution of **5** was allowed to stand at room temperature for 24 h. After lyophilisation, the solid residue was analysed in $D_2O$ solution by $^1H$ and $^{13}C$ NMR spectroscopy. The sample had been completely transformed, giving a complex series of signals, which indicated, notably, the disappearance of the C1 and C2 cyclobutane ring methine centres, and the appearance of two new types of signal corresponding to an aldehyde ($\delta_H$ 9.11 ppm; $\delta_C$ 198.9 ppm) and an iminium ($\delta_H$ 6.64 ppm; $\delta_C$ 159.8 ppm). The *J*-modulated $^{13}C$ spectra of **5** and of the sample obtained from **5** by ageing are presented in Figure 1 (above and below, respectively).

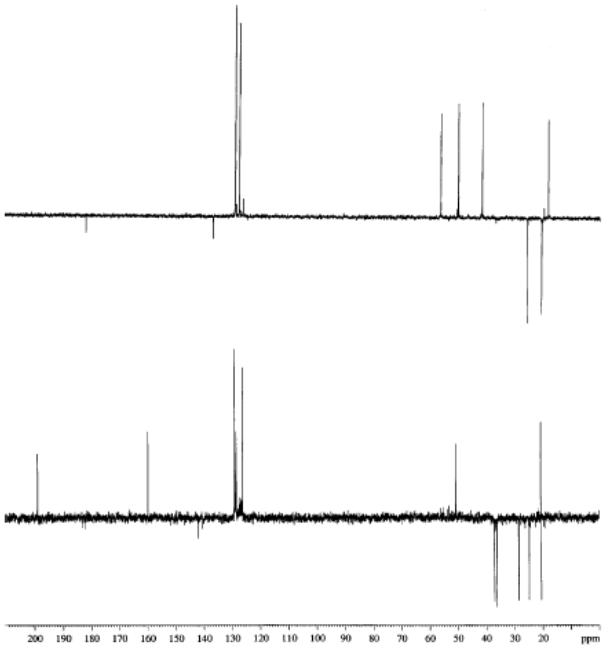
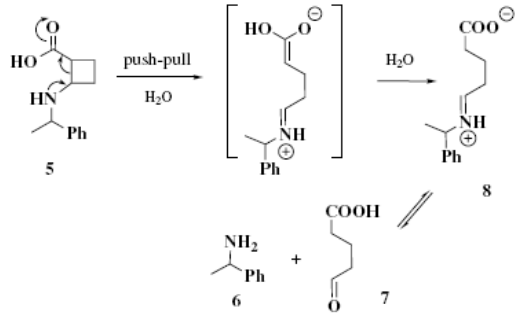



**Figure 1.** *J*-Modulated $^{13}C$ NMR spectra of fresh **5** (above) and aged **5** (below).




**Scheme 4.**

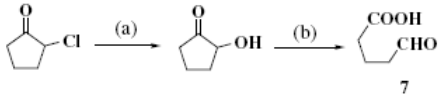
We interpreted these data in terms of an equilibrium mixture of three components: α-methylbenzylamine **6**, 5-oxopentanoic acid **7**, and the iminium **8** obtained by condensation of **6** and **7** (Scheme 4). Formation of the iminium could be explained by a spontaneous 'push-pull' induced ring opening to generate an enolate.[8] Reprotonation of the latter by the solvent would lead to **8** and hence to the final mixture. Support for this argument was obtained by ageing **5** for 24 h in $D_2O$ solution. The same NMR spectral data were observed in this case, except that the carbon atom giving rise to the

signal at $\delta_C$ 36.1 ppm (putatively α- to the carboxylate) was monodeuterated.

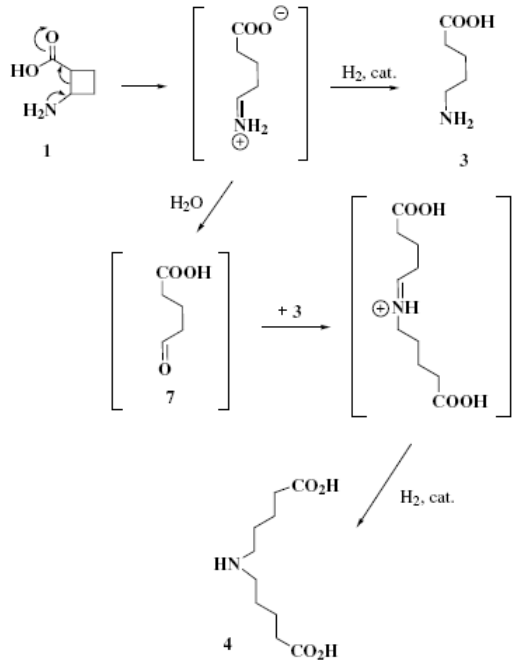
Confirmation of the above hypothesis was obtained independently as follows. 5-Oxopentanoic acid **7** was prepared in two steps from commercial 2-chlorocyclopentanone in an adaptation of previous work[9] (Scheme 5). Equimolar amounts of **7** and commercial (±)-α-methylbenzylamine were dissolved together in $D_2O$, and the NMR spectra recorded after 30 min. Data were identical to those obtained for the sample of **5**, which had been aged in aqueous solution (for example, the *J*-modulated $^{13}C$ NMR spectrum was identical to the lower one in Fig. 1).

The facile formation of **3** and **4** from **1** or **2** under hydrogenation conditions is thus rationalised: the iminium intermediate formed in solution by ring opening can be simply reduced to the corresponding amine **3**. Alternatively, it can undergo hydrolysis to give the corresponding aldehyde **7**, which condenses with already-formed amine **3** giving a new iminium, which is in turn reduced to **4** (Scheme 6).

This work illustrates and underlines the propensity for the cyclobutane β-aminoacid skeleton to undergo ring opening in mild conditions. The proposed mechanism is formally a retro-Mannich type process and is reminiscent of certain azo-de Mayo fragmentations of bicyclic β-aminoketones.[10] This appears to be the first demonstration of analogous behaviour by the cyclobutane β-aminoacid skeleton.[11] In the light of these results, appropriate care is cautioned in the preparation and use of such compounds and in the interpretation of physicochemical data obtained or reported for them.




**Scheme 5.** Reagents and conditions: (a) $H_2O$, 100 °C, 1 h, 83%; (b) $NaIO_4$, THF–$H_2O$, rt, 16 h, 100%.




**Scheme 6.**

## Acknowledgements

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## References and notes

1. Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2002**, *43*, 6177–6179.
2. Kennewell, P. D.; Matharu, S. S.; Taylor, J. B.; Westwood, R.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2563–2570.
3. Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Alvarez-Larena, A.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3569–3584.
4. (a) Izquierdo, S.; Martín-Vilà, M.; Moglioni, A. G.; Branchadell, V.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2403–2405; (b) Panda, J.; Ghosh, S.; Ghosh, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3013–3016; (c) Yuan, P.; Driscoll, M. R.; Raymond, S. J.; Hansen, D. E.; Blatchley, R. A. *Tetrahedron Lett.* **1994**, *35*, 6195–6198; (d) Mitsudo, T.; Zhang, S.-W.; Satake, N.; Kondo, T.; Watanabe, Y. *Tetrahedron Lett.* **1992**, *33*, 5533–5536.
5. Spectroscopic data for compound **4**: $\delta_H$ ($D_2O$) 1.66 (8H, m), 2.31 (4H, t, $J = 6.8$ Hz), 3.04 (4H, t, $J = 6.8$ Hz); $\delta_C$ ($D_2O$) 21.9 ($CH_2$), 25.1 ($CH_2$), 35.0 ($CH_2$), 47.1 ($CH_2$), 180.7 ($C_q$); ESMS $m/z$ 218 $[MH]^+$.
6. Bisel, P.; Breitling, E.; Frahm, A. W. *Eur. J. Org. Chem.* **1998**, 729–733.
7. Compound **5** was prepared from racemic 1-(α-methylbenzyl)uracil, via a [2+2] photocyclisation reaction with ethylene then hydrolysis of the heterocyclic moiety, according to Ref. 1, and was used as a single (racemic) diastereomer. Full details of the interest of this and similar structures in the asymmetric synthesis of **1** will appear in a future full paper.
8. Ring opening processes of donor–acceptor substituted cyclopropanes are well documented: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196; (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1623.
9. (a) Godchot, M.; Taboury, F. *C.R. Hebd. Séances Acad. Sci.* **1913**, *156*, 332–334; (b) Floresca, R.; Kurihara, M.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 2196–2200.
10. For leading references on aza-de Mayo reactions, see the appropriate sections in: (a) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003–2020; (b) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1435–1473.
11. Very recently the ring expansion of a strained tricyclic 4-aminocyclobutenecarboxylate system was described: Mislin, G. L.; Miesch, M. *J. Org. Chem.* **2003**, *68*, 433–441; See also: Adembri, G.; Donati, D.; Fusi, S.; Ponticelli, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2033–2038.